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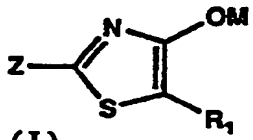

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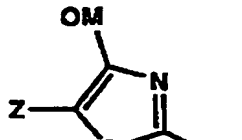

(II)

(57) Abstract

Compounds of formulae (I) and (II), and pharmaceutically acceptable salts, esters and prodrugs thereof, wherein M and R_1 are independently selected from among optionally substituted alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, reduced heteroaryl and reduced heteroarylalkyl groups, and Z is the residue of a compound selected from the class of compounds known as non-steroidal antiinflammatory drugs containing a carboxylic acid group, of the general form Z-COOH.

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THIAZOLE LIPOXYGENASE-INHIBITING COMPOUNDS DERIVED FROM NON-STEROIDAL ANTIINFLAMMATORY CARBOXYLIC ACIDS

Technical Field

This invention relates to inhibitors of lipoxygenase enzymes, and more particularly to novel lipoxygenase-inhibiting thiazole compounds which are derived from non-steroidal antiinflammatory drugs (NSAID) containing the carboxylic acid functionality. It also relates to methods and compositions for inhibiting lipoxygenase enzymes in humans and animal hosts in need of such treatment.

Background of the Invention

5-Lipoxygenase is the first enzyme in the pathway leading to the biosynthesis of leukotrienes (LTs). In the course of this pathway or "cascade", arachidonic acid, the 5-lipoxygenase substrate from which leukotriene (LT) products are derived, is first converted to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) and subsequently reduced to 5-hydroxyeicosatetraenoic acid (5-HETE) or converted to LTA_4. The reactive leukotriene intermediate LTA_4 is enzymatically hydrated to LTB_4 or conjugated to the tripeptide glutathione to produce LTC_4. LTA_4 can also be hydrolyzed nonenzymatically to form two isomers of LTB_4. Successive proteolytic cleavage steps convert LTC_4 to LTD_4 and LTE_4. Other products resulting from further oxygenation steps have also been described. (See Serhan, C.N., Hamberg, M., and Samuelsson, B., Lipoxins: Novel Series of Biologically Active Compounds Formed from Arachidonic Acid in Human Leukocytes, Proceedings of the National Academy of Sciences, USA, 81:5335 (1985)).

Products of the 5-lipoxygenase cascade are extremely potent substances which produce a wide variety of biological effects, often in the nanomolar to picomolar concentration range. (Sirois, P., "Pharmacology of the Leukotrienes", Advances in Lipid Research, R. Paoletti & D. Kritchevesky, eds., Academic Press, 21:79 (1985.)) The remarkable potencies and diversity of actions of products of the 5-lipoxygenase pathway have led to the suggestion that they play important roles in a variety of diseases. The presence of LTs A_4-E_4 has been associated with a number of disease states, including asthma, allergic rhinitis, rheumatoid arthritis, gout, psoriasis, inflammatory disorders of the skin, acne, atherosclerosis, adult respiratory distress syndrome, inflammatory bowel disease, endotoxin shock, ischemia-induced myocardial injury, and central nervous pathophysiology.

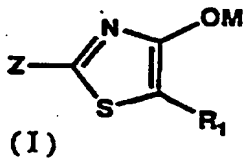
The enzyme 5-lipoxygenase catalyzes the first step leading to the biosynthesis of all the leukotrienes, and inhibition of this enzyme is therefore likely to limit the effects of these potent mediators of numerous patho-physiological processes. Agents which block or modulate the activity of lipoxygenase enzymes thus represent a promising class of therapeutic agents for use in the treatment of diseases involving leukotriene pathogenesis. (Brooks, D.W., Bell, R.L., and Carter, G.W., Chapter 8: Pulmonary and Antiallergy Agents, Annual Reports in Medicinal Chemistry, Allen, R.C., ed., Academic Press (1988)). Examples of 5-lipoxygenase inhibitors known to the art are: AA-861, disclosed in U.S. Patent 4,393,075, issued July 12, 1983 to Terro et al.; pyrazolopyridines, disclosed in the European Patent Application of Iriburn et al., Ser. No. 121,806, published October 17, 1984; arachidonyl hydroxamic acid, disclosed in Corey et al., J. Am. Chem. Soc., 106:1503 (1984) and in the European Patent Application of Nelson, Ser. No. 104,468, published April 4, 1984; BW-755C, disclosed in Radmark et al., FEBS Letters,

110:213 (1980); nordihydroguaiaretic acid, disclosed in Marris et al., Prostaglandins, 19:371 (1980); Rev-5901, disclosed in Coutts, Meeting Abstract 70, Prostaglandins and Leukotrienes '84; benzoxaprofen, disclosed in Walker, Pharm. Pharmacol., 31:778 (1979); and hydroxamic acids, disclosed in U.S. Patents Nos. 4,608,390 and 4,623,661, issued August 16 and November 18, 1986, respectively.

Summary of the Invention

The present invention comprises compounds which exhibit unexpected activity as inhibitors of lipoxygenase enzymes, particularly 5-lipoxygenase, and thereby reduce the biosynthesis of leukotrienes LTB_4, LTC_4, LTD_4 and LTE_4. Also disclosed is a method of inhibiting 5- and/or 12-lipoxygenase activity in a mammal in need of such treatment by administering to such a mammal the inventive compounds in an amount effective to inhibit lipoxygenase activity.

One aspect of the present invention is the group of compounds having the formulae:



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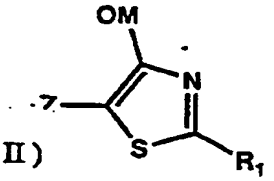
and



(II)

and pharmaceutically acceptable salts, esters and prodrugs thereof.

In these compounds R_1 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, reduced heteroaryl, reduced heteroarylalkyl, and substituted derivatives thereof. Substituents may be independently chosen from the group consisting of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, reduced heteroaryl, arylalkoxy, cyano, nitro, $-SO_2R_4$, $-C(O)R_4$, $-NR_5R_6$, $-OR_6$,

$-C(O)CX_1X_2NR_6R_7$, $-C(O)N(OH)R_6$, $-NR_6C(O)R_4$, $-CR_5(NH_2)CO_2R_5$, $-NHCX_1X_2CO_2R_5$, $-N(OH)C(O)NR_5R_6$, $-N(OH)C(O)R_4$, $-NHC(O)NR_5R_6$, $-C(NOH)NHOH$, and $-C(O)NHNR_5R_6$.

R_4 is independently selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced heteroaryl, reduced heteroarylalkyl, $-OR_5$, an amino residue of formula $-NHCX_1X_2CO_2R_5$, and $-NR_6R_7$.

R_5 is independently selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, reduced heteroaryl, and reduced heteroarylalkyl.

R_6 and R_7 are independently selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, reduced heteroaryl, reduced heteroarylalkyl, and $-(CH_2)_nOR_5$ wherein n is 2 to 4.

X_1 and X_2 are independently selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, aryl, and arylalkyl.

M is selected from the group consisting of hydrogen, a pharmaceutically acceptable salt, $-C(O)R_4$, $-C(O)CX_1X_2NR_6R_7$, $-CR_8R_9OR_{10}$, $-CH_2CR_8(OR_{10})CH_2OR_{11}$, and $-SiR_{12}R_{13}R_{14}$.

R_8, R_9, R_{10} and R_{11} are independently selected at each occurrance from the group consisting of hydrogen, alkyl, aryl, arylalkyl, and $-(CH_2)_nOR_5$ wherein n is 2 to 4. Alternatively, at least two of R_8, R_9, R_{10} and R_{11} together can form a carbocyclic or heterocyclic or reduced heterocyclic ring system containing 5-10 atoms.

R_{12}, R_{13} and R_{14} are independently selected at each occurrance from the group consisting of alkyl and aryl.

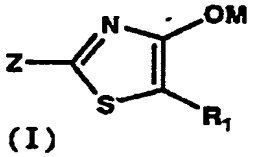
Z is the residue of a compound selected from the class of compounds known as non-steroidal antiinflammatory drugs containing a carboxylic acid group, of the general form Z-COOH.

Another aspect of the present invention is the group of compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of one of the above inventive compounds.

Yet another aspect of the invention is a method for treating asthma, allergic rhinitis, rheumatoid arthritis, gout, psoriasis, acne, atherosclerosis, adult respiratory distress syndrome, inflammatory bowel disease, endotoxin shock, ischemia-induced myocardial injury, or central nervous pathophysiology in a mammal in need of such treatment.

Detailed Description of the Invention

The novel compounds of this invention are those of Formula I and Formula II:



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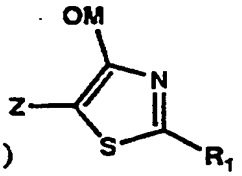


(II)

and pharmaceutically acceptable salts, esters and prodrugs thereof.

R_1 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, reduced heteroaryl, reduced heteroarylalkyl, and substituted derivatives thereof with one or more substituents independently chosen from the group consisting of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, reduced heteroaryl, arylalkoxy, cyano, nitro, $-SO_2R_4$, $-C(O)R_4$, $-NR_5R_6$, $-OR_6$, $-C(O)CX_1X_2NR_6R_7$, $-C(O)N(OH)R_6$, $-NR_6C(O)R_4$, $-CR_5(NH_2)CO_2R_5$, $-NHCX_1X_2CO_2R_5$, $-N(OH)C(O)NR_5R_6$, $-N(OH)C(O)R_4$, $-NHC(O)NR_5R_6$, $-C(NOH)NHOH$, and $-C(O)NHNR_5R_6$.

R_4 is selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced heteroaryl, reduced

heteroarylalkyl, $-OR_5$, an amino residue of formula $-NHCX_1X_2CO_2R_5$, and $-NR_6R_7$.

R_5 is selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, reduced heteroaryl, and reduced heteroarylalkyl.

R_6 and R_7 are independently selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, reduced heteroaryl, reduced heteroarylalkyl, and $-(CH_2)_nOR_5$ wherein n is 2 to 4.

X_1 and X_2 are independently selected at each occurrance from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, aryl, and arylalkyl.

M is selected from the group consisting of hydrogen, a pharmaceutically acceptable salt, $-C(O)R_4$, $-C(O)CX_1X_2NR_6R_7$, $-CR_8R_9OR_{10}$, $-CH_2CR_8(OR_{10})CH_2OR_{11}$, and $-SiR_{12}R_{13}R_{14}$.

R_8, R_9, R_{10} and R_{11} are independently selected at each occurrance from the group consisting of hydrogen, alkyl, aryl, arylalkyl, and $-(CH_2)_nOR_5$ wherein n is 2 to 4. Alternatively, at least two of R_8, R_9, R_{10} and R_{11} together can form a carbocyclic or heterocyclic or reduced heterocyclic ring system containing 5-10 atoms.

R_{12}, R_{13} and R_{14} are independently selected at each occurrance from the group consisting of alkyl and aryl.

Z is the residue of a compound selected from the class of compounds known as non-steroidal antiinflammatory drugs containing a carboxylic acid group, of the general form Z-COOH.

Compounds considered within the classification of non-steroidal antiinflammatory drugs (NSAID) have been documented by J. Lombardino in "Nonsteroidal Antiinflammatory Drugs", Wiley-Interscience, New York, 1985. Examples of compounds of this class of

antiinflammatory drugs include but are not limited to the following:

(1) benoxaprofen,
(2) benzofenac,
(3) bucloxic acid,
(4) butibufen,
(5) carprofen,
(6) cicloprofen,
(7) cinmetacin,
(8) clidanac,
(9) clopirac,
(10) diclofenac,
(11) etodolac,
(12) fenbufen,
(13) fenclofenac,
(14) fenclorac,
(15) fenoprofen,
(16) fentiazac,
(17) flunoxaprofen,
(18) furaprofen,
(19) furobufen,
(20) furofenac,
(21) ibuprofen,
(22) ibufenac,
(23) indomethacin,
(24) indoprofen,
(25) isoxepac,
(26) ketoprofen,
(27) lonazolac,
(28) metiazinic,
(29) miroprofen,
(30) naproxen,
(31) oxaprozin,
(32) oxepinac,
(33) pirprofen,

(34) pirazolac,
(35) protizinic acid,
(36) sulindac,
(37) suprofen,
(38) tiaprofenic acid,
(39) tolmetin, and
(40) zomepirac.

Examples of compounds which are themselves within the scope of the present invention and/or can be used according to the methods of the present invention include, but are not limited to, the following:

2-[1-(6-methoxy-2-naphthyl)ethyl]-5-phenyl-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)ethyl]-5-phenyl-4-hydroxythiazole,
2-[(4-isobutylphenyl)methyl]-5-phenyl-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-phenyl-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole,
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-(4-methoxyphenyl)-4-hydroxythiazole,
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-(4-carbomethoxy-phenyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-methoxyphenyl)--4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-methoxycarbonyl-phenyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-fluorophenyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(2,4-difluorophenyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(propyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(1-ethylphenyl)-4-hydroxythiazole,

2-[1-(4-isobutylphenyl)propyl]-5-(1-ethenylphenyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-cyclohexyl-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-cyclopropyl-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(thien-2-yl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(methylthien-2-yl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-[3-(ethoxycarbonyl)-propyl]-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-N-methyl-N-hydroxyamidobutyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-hydroxybutyl)-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-acetylthiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-hydroxythiazole potassium salt,
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-trimethylsilyloxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-glycinylthiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-succinylthiazole,
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-succinyl-N-methyl-N-hydroxyamidothiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-fluorophenyl-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2,4-difluorophenyl-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-methoxyphenyl-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(thien-3-yl)-4-hydroxythiazole,

5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-pyridyl)-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-pyridyl)-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-benzothienyl)-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-benzothiazoyl)-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-thiazoyl)-4-hydroxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-acetoxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole potassium salt,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-methoxycarbonyloxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-N-methyl-N-hydroxycarbonyl-oxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-succinylthiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-[1-(4-isobutyl-phenyl)ethyl]-4-acetoxythiazole,
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-[1-(4-isobutyl-phenyl)propyl]-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)ethyl]-5-[1-(4-isobutylphenyl)-ethyl]-4-hydroxythiazole,
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-[1-(4-isobutyl-phenyl)ethyl]-4-hydroxythiazole,
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-[1-(4-isobutyl-phenyl)ethyl]-4-benzoylthiazole,
2-[1-(4-phenoxyphenyl)ethyl]-5-phenyl-4-hydroxythiazole],
2-[1-(2-(4-chlorophenyl)benzoxaz-5-yl)ethyl]-5-phenyl-4-hydroxythiazole,
2-[2-(4,5 diphenyloxaz-2-yl)ethyl]-5-phenyl-4-hydroxythiazole,
2-[2-(N-methyl-9-methoxyphenothiazin-4-yl)ethyl]-5-phenyl-4-hydroxythiazole, and

2-[5-fluoro-2-methyl-(4-methylsulfinylbenzylidene)-inden-3-ylmethyl]-5-phenyl-4-hydroxythiazole.

Preferred compounds of the present invention include, but are not limited to, the following:

2-[1-(6-methoxy-2-naphthyl)ethyl]-5-phenyl-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)ethyl]-5-phenyl-4-hydroxythiazole,
2-[(4-isobutylphenyl)methyl]-5-phenyl-4-hydroxythiazole,
2-[1-(4-isobutylphenyl)propyl]-5-phenyl-4-hydroxythiazole, and
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole.

The compounds of the present invention can also be prepared in the form of pharmaceutically acceptable salts, esters and other prodrugs. Derivative salts include relatively non-toxic inorganic or organic acid addition salts or alkaline earth metal salts of the inventive compounds, which can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the free base with a suitable organic or inorganic acid. Where the compounds include a basic functionality such as an amine or alkylamine, representative salts include hydrochloride, sulfate, acetate, maleate, lauryl sulphate and the like. Where an acidic functionality is present, salts such as sodium, calcium, potassium and magnesium salts may be formed.

Pharmaceutically acceptable esters and other prodrugs of the inventive compounds can be prepared by methods known in the art, such as those described in "Design of Prodrugs", Bundgaard, H., ed., Elsevier, Amsterdam, pp. 1-92 (1985). These prodrugs, which are

formed by the addition of a metabolically cleavable group to compounds bearing a hydroxyl or carboxyl functionality, are converted in vivo to the parent compound and may provide improved absorption and bioavailability. Examples of such esters include glycyl, lysyl, acetyl and succinyl derivatives, while other prodrugs may be formed by the addition, for example, of alkanoyl, aroyl, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl and silyl groups.

The term "alkyl" as used herein refers to a straight or branched chain radical containing 1 to 6 carbon atoms including, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl.

The term "alkylene" as used herein refers to a straight or branched chain intervening radical containing 1 to 6 carbon atoms including, but not limited to, $-CH_2-$, $-CH(CH_3)-$, $-CH(C_2H_5)-$, $-CH(CH_3)CH_2-$ and $-(CH_2)_3-$.

The term "alkenyl" as used herein refers to a straight or branched chain radical containing 2 to 6 carbon atoms and a carbon-carbon-double bond including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl and 2-butenyl.

The term "alkenylene" as used herein refers to a straight or branched chain intervening radical containing 2 to 6 carbon atoms and a carbon-carbon double bond, including, but not limited to, $-CH=CH-$, $-C(CH_3)=CH-$, $-CH=CH-CH_2-$, $-CH=C(CH_3)-CH_2-$ and $-CH_2CH(CH=CH_2)CH_2-$.

The term "cycloalkyl" as used herein refers to cyclic radicals of 3 to 8 carbons, including, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The terms "alkoxy" and "thioalkoxy" as used herein

refer to $-OR_{15}$ and $-SR_{15}$, respectively, wherein R_{15} is an alkyl group, including, but not limited to, methoxy, ethoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, tert-butoxy, methylthio, ethylthio, isopropylthio, n-butylthio and tert-butylthio.

The term "alkylamino" as used herein refers to $-NHR_{16}$ wherein R_{16} is an alkyl group.

The term "dialkylamino" as used herein refers to $-NR_{17}R_{18}$ wherein R_{17} and R_{18} are the same or different alkyl groups.

The term "aminocarbonyl" as used herein refers to $-C(O)NH_2$.

The term "alkylaminocarbonyl" as used herein refers to $-C(O)NHR_{19}$ wherein R_{19} is an alkyl group.

The term "dialkylaminocabonyl" as used herein refers to $-C(O)NR_{20}R_{21}$ wherein R_{20} and R_{21} are the same or different alkyl groups.

The term "alkoxycarbonyl" as used herein refers to $-C(O)OR_{22}$ wherein R_{22} is an alkyl group.

The term "alkanoyl" as used herein refers to $-C(O)R_{23}$ wherein R_{23} is hydrogen or an alkyl group including, but not limited to, formyl, acetyl, propionyl, butyryl, isobutyryl and pivaloyl.

The term "carbocyclic" as used herein refers to saturated cyclic groups of three to six carbon atoms including, but not limited to, cyclopentyl and cyclohexyl.

The term "heterocyclic" as used herein refers to an unsaturated single- and fused-ring group of three to twelve atoms containing one or more heteroatoms selected from N, O and S including, but not limited to, thienyl, furanyl, thiazolyl, pyridyl, pyrimidyl, oxazolyl, benzothienyl, benzofuranyl, benzothiazolyl, indolyl, quinolyl and isoquinolyl.

The term "reduced heterocyclic" as used herein refers to a partially or completely hydrated

heterocyclic group including, but not limited to, dihydrothienyl, tetrahydrothienyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothiazole, tetrahydrothiazole, dihydroindolyl, tetrahydroindolyl, dihydroquinolyl and tetrahydroquinolyl.

The term "aryl" as used herein refers to a substituted or unsubstituted carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2-naphthyl, and the like, and refers also to a substituted or unsubstituted heterocyclic aromatic group wherein the heterocyclic aromatic group is a 5- or 6-membered aromatic ring containing from one to three heteroatoms independently selected from oxygen, sulfur and nitrogen. The term "aryl" also includes bicyclic groups in which any of the above heterocyclic aromatic rings, including, but not limited to, furanyl, thienyl, pyridyl, indolyl, quinolyl and benzimidazolyl, is fused to a benzene ring. Substituted aryl groups can be substituted with one or two substituents independently selected from hydroxy, halo, alkoxy, thioalkoxy, alkyl, nitro, amino, alkylamino, dialkylamino, haloalkyl, cyano, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl and dialkylaminocarbonyl.

The term "reduced heteroaryl" as used herein refers to a partially or completely hydrated heteroatom-containing aryl group including, but not limited to, dihydrothienyl, tetrahydrothienyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyridyl, tetrahydropyridyl, dihydroquinolyl, tetrahydroquinolyl, dihydroindolyl and tetrahydroindolyl.

The term "aroyl" as used herein refers to $-C(O)R_{24}$ wherein R_{24} is an aryl group including, but not limited to, benzoyl, 1-naphthoyl, 2-naphthoyl and 2-furoyl.

The term "aryloxy" as used herein refers to

$-OR_{25}$ wherein R_{25} is an aryl group including, but not limited to, phenoxy, 1-naphthoxy and 2-naphthoxy.

The term "arylalkyl" as used herein refers to an aryl group appended to an alkyl radical including, but not limited to, phenylmethyl (benzyl), 2-phenylethyl, 1-naphthylmethyl, 2-pyridylmethyl and 2-quinolylmethyl.

The term "reduced heteroarylalkyl" as used herein refers to a reduced heteroaryl group appended to an alkyl radical including, but not limited to, dihydrothienylmethyl, tetrahydrothienylmethyl, dihydropyranylmethyl, tetraphydropyranylmethyl, dihydroquinolylethyl and tetrahydroquinolylethyl.

The terms "arylalkoxy" and "arylthioalkoxy" as used herein refer to $-OR_{26}$ and $-SR_{26}$, respectively, wherein R_{26} is an arylalkyl group including, but not limited to, phenylmethoxy (i.e., benzyloxy), 1-phenylethoxy, 2-phenylethoxy, 1-naphthylmethyloxy, 2-napthylmethyloxy, 2-, 3- or 4-pyridylmethoxy, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolylmethoxy, benzylthio, 1-phenylthio, 2-phenylthio, 1-naphthylmethylthio, 2-naphthylmethylthio, and 2-, 3- or 4-pyridylmethylthio.

The term "arylalkenyl" as used herein refers to an aryl group appended to an alkenyl radical including, but not limited to, phenylethenyl, 3-phenylprop-1-enyl, 3-phenylprop-2-enyl, 1-naphthylethenyl and 3-pyrid-3-yl-prop-1-enyl.

The terms "halo" and "halogen" as used herein refer to radicals derived from the elements fluorine, chlorine, bromine, and iodine.

The terms "halosubstituted alkyl" and "haloalkyl" as used herein refer to an alkyl group in which one or more hydrogen atoms are substituted by a halogen and include, but are not limited to, chloromethyl, trifluoromethyl and 2,2,2-trichloroethyl.

The term "pharmaceutically acceptable salt" as used herein refers to a relatively non-toxic,

inorganic or organic acid addition salt of the compounds of the invention including, but not limited to, hydrochloride, hydrobromide, sulfate, nitrate, bisulfate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate and lauryl sulphate as well as to alkali or alkaline earth salts including, but not limited to, sodium, calcium, potassium and magnesium.

The term "pharmaceutically acceptable cation" refers to non-toxic cations including, but not limited to, those based on the alkali and alkaline earth metals such as sodium, lithium, potassium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium and amine cations, including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine and ethylamine.

The term "ester" as used herein refers to a hydroxyl- or carboxyl-substituted derivative of a compound of the present invention in which the substituting group is a metabolically cleavable group including, but not limited to, glycyl, lysyl, acetyl and succinyl.

The term "prodrug" as used herein refers to a hydroxyl- or carboxyl-substituted derivative of a compound of the present invention in which the substituting group is a metabolically cleavable group including, but not limited to, alkanoyl, aroyl, aminocarbonyl, alkylaminocarbonyl, alkoxycarbonyl and silyl.

The term "residue" as used herein with respect to a non-steroidal antiinflammatory carboxylic acid compound refers to that portion of the

antiinflammatory compound which remains after removal of the -COOH portion of the molecule.

Certain compounds of this invention can exist in optically active forms. The R and S isomers and racemic mixtures thereof, as well as mixtures of cis and trans isomers, are contemplated by this invention. Additional assymetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention.

Method of Treatment

This invention provides a method of treatment of inhibiting 5- and/or 12-lipoxygenase activity in a human or lower mammal host in need of such treatment which method comprises administering to the human or lower mammal host one of the compounds previously described herein in an amount effective to inhibit lipoxygenase activity in the host. The compounds of the present invention may be administered orally, parenterally or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants and vehicles as desired.

The term "parenterally" as used herein includes subcutaneous, intravenous, intraarterial injection or infusion techniques, without limitation. The term "topically" encompasses administration rectally and by inhalation spray, as well as by the more common routes of the skin and the mucous membranes of the mouth and nose.

Total daily dose of the compounds of this invention administered to a host in single or divided doses may be in amounts, for example, of from about 0.001 to about 100 mg/kg body weight daily and more usually 0.01 to 10 mg/kg/day. Dosage unit

compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including body weight, general health, sex, diet, time and route of administration, rates of absorption and excretion, combination with other drugs and the severity of the particular disease being treated.

Formulation of Pharmaceutical Composition

This invention also provides for compositions in unit dosage form for the inhibition of 5- or 12-lipoxygenase activity in a human or lower mammal host in need of such treatment, comprising a compound of this invention and one or more nontoxic pharmaceutically acceptable carriers, adjuvants or vehicles. The amount of active ingredient that may be combined with such materials to produce a single dosage form will vary depending upon various factors, as indicated above.

A variety of materials can be used as carriers, adjuvants and vehicles in the composition of this invention, as available in the pharmaceutical arts. Injectable preparations, such as oleaginous solutions, suspensions or emulsions, may be formulated according to known art, using suitable dispersing or wetting agents and suspending agents, as needed. The sterile injectable preparation may employ a nontoxic parenterally acceptable diluent or solvent as, for example, sterile nonpyrogenic water or 1,3-butanediol. Among the other acceptable vehicles and solvents that may be employed are 5% dextrose injection, Ringer's injection and isotonic sodium chloride injection (as described in the USP/NF). In addition, sterile, fixed oils are conventionally

employed as solvents or suspending media. For this purpose any bland fixed oil may be used, including synthetic mono-, di- or triglycerides. Fatty acids such as oleic acid can also be used in the preparation of injectable compositions.

Suppositories for rectal administration of the compound of this invention can be prepared by mixing the drug with suitable nonirritating excipients such as cocoa butter and polyethylene glycols, which are solid at ordinary temperatures but liquid at body temperature and which therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration include capsules, tablets, pills, troches, lozenges, powders and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, pharmaceutical adjuvant substances, e.g., stearate lubricating agents. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Solid oral preparations can also be prepared with enteric or other coatings which modulate release of the active ingredients.

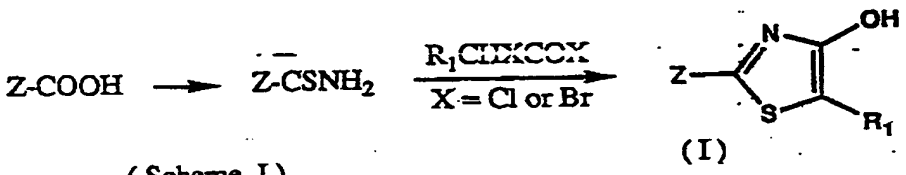
Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert nontoxic diluents commonly used in the art, such as water and alcohol. Such compositions may also comprise adjuvants, such as wetting, emulsifying, suspending, sweetening, flavoring and perfuming agents.

Synthesis of the Compounds

Compounds of this invention can be prepared by the processes presented hereinbelow. In certain cases where the non-steroidal antiinflammatory drug (NSAID)

contains functional groups which might interfere with a desired transformation outlined in the following processes, it is recognized that common methods of protection of these groups followed by deprotection at a later stage in the preparation of the desired product can be employed. A general reference source for methods of protection and deprotection is T. W. Greene, "Protective Groups in Organic Synthesis", Wiley-Interscience, New York, 1981.

4-Hydroxythiazoles of Formula I are prepared by the reaction sequence outlined in Scheme I, below. The nonsteroidal antiinflammatory drugs, Z-CO_2H, are converted to the corresponding thioamides by a sequence of known methods, for example, by successive treatment with a) thionyl chloride, b) ammonium hydroxide, and c) Lawesson's reagent. The thioamides are then reacted with an alpha-haloester or alpha haloacid chloride or alpha haloacid bromide at high temperature in toluene to provide the corresponding 4-hydroxythiazoles.

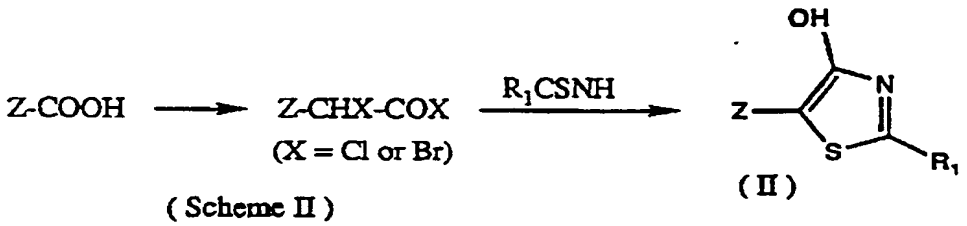


(I)

(Scheme I)

4-Hydroxythiazoles of Formula II are prepared by the reaction sequence outlined in Scheme II. The nonsteroidal antiinflammatory drugs, Z-CO_2H, are converted to the corresponding homologous acid Z-CH_2CO_2H by known methods. For example, the following references describe applicable methods: Kowalski, C.J., Haque, M.S., Fields, K.W., J. Am. Chem. Soc., 107:1429 (1985); Johnson, W.S.,

Christiansen, R.G., Ireland, R.E., J. Am. Chem. Soc., 79:1995 (1957); Dinizo, S.E., Freerksen, R.W., Pabst, W.E., Watt, D.S., J. Am. Chem. Soc., 99:182 (1977). Conversion to the alpha-halo acid halide analog Z-CHX-COX where X = Cl or Br also is accomplished by known methods. Reaction of the alpha-haloacid halide with a thioamide compound provides the desired hydroxythiazole.



(Scheme II) (II)

Other known methods to access the intermediate Z-CHX-COX from starting materials other than NSAID carboxylic acids substrates are also taught by Example 5.

The following examples are for the purpose of illustrating the use of the above synthetic schemes to prepare representative compounds or the present invention, and are not intended to limit the scope of the claims in any way.

Example 1. 2-[1-(6-methoxy-2-naphthyl)ethyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 1-(6-methoxy-2-naphthyl)ethyl, R_1= phenyl, M= H).

Oxalyl chloride (1.9 mL, 22 mmol) was added dropwise to naproxen (5g, 22 mmol) in methylene chloride (100 mL) at 5°C under nitrogen, and N,N-Dimethylformamide (0.02 mL) was added to catalyze the reaction. The reaction mixture was allowed to warm to 23°C and stirred for 8 hours. Concentrated ammonium

hydroxide (10 mL) was added to the cooled (5°C) solution. After 1 hour at 23°C the reaction mixture was concentrated in vacuo and water (200 mL) was added. The precipitate was collected and recrystallized from methylene chloride/methanol to afford the pure amide (4.2 g, 85%), mp 177-178°C. ^{1}H NMR (60 MHz, DMSO-d_6) 1.41 (3H, d, J=7 Hz), 3.65 (1H, q, J=7Hz), 3.80 (3H, s), 6.72 (2H, br s), 7.1-7.8 (6H, m); MS: 229 (M+).

Anal. Calc'd for $C_{14}H_{15}NO_2$: C,73.36; H, 6.55; N, 6.11.

Found: C,73.69; H,6.58; N, 6.01.

Lawesson's reagent (3.6 g, 9 mmol) was added to the amide (4 g, 18 mmol) suspended in toluene (200 mL) at 23°C under nitrogen. The reaction mixture was then heated at 100°C for 2 hours. After cooling to 23°C, the organic solvent was evaporated and the crude residue chromatographed (silica gel, chloroform) to afford the thioamide (1.4 g, 33%).

mp 144-145°C; ^{1}H NMR (60MHz, DMSO-d_6) 1.55 (3H, d, J=7Hz), 3.81 (3H, s), 4.11 (1H, q, J=7 Hz), 7.05-7.85 (8H, m); MS: 245 (M+)

Anal. Calc'd for $C_{14}H_{15}NOS$: C, 68.57; H, 6.12; N, 5.71.

Found: C, 68.19; H, 6.12; N, 5.75.

Alpha-Chlorophenylacetylchloride (0.65 mL, 4.1 mmol) was added dropwise to the thioamide (1.0 g, 4 mmol) in toluene (100 mL) containing pyridine (0.65 mL, 8 mmol) under nitrogen. The reaction mixture was then heated at 108°C for 4 hours. The reaction mixture was cooled and the solvent evaporated. Recrystallization from ether/ethanol provided the title compound (0.3 g, 27%).

mp 245-246°C; ^{1}H NMR (60 MHz, DMSO-d_6): 1.61 (3H, d, J=7Hz), 3.81 (3H, s), 4.21 (1H, q, J=7Hz), 7.1-8.0 (11H, m), 10.41 (1H, s); MS: 361 (M+)

Anal. Calc'd for $C_{22}H_{19}NO_2S$: C, 73.13; H, 5.26; N, 3.88.
Found: C, 73.28; H, 5.24; N, 3.92.

Example 2. 2-[1-(4-isobutylphenyl)ethyl]-5-phenyl-4-hydroxy-thiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)ethyl], R_1= phenyl, M= H).

The title compound was prepared according to the method of Example 1 except that ibuprofen was used instead of naproxen.
mp 185-186°C; ^{1}H NMR (60MHz, DMSO-d_6): 0.85 (6H, d, J=7Hz), 1.60 (3H, d, J=7Hz), 1.85 (1H,m), 2.45 (2H, d, J=7Hz), 4.01 (1H, q, J=7Hz), 7.0-8.0 (9H,m), 10.27 (1H,s); MS: 337 (M+)
Anal. Calc'd. for $C_{21}H_{23}NOS$: C, 74.78; H, 6.82; N, 4.54.
Found: C, 74.39: H, 6.85: N, 4.51.

Example 3. 2-[(4-isobutylphenyl)methyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 2-[(4-isobutylphenyl)-methyl], R_1= phenyl, M= H).

The title compound was prepared according to the method of Example 1 except that ibufenac was used instead of naproxen.
mp 196-197°C; ^{1}H NMR (60 MHz, DMSO-d_6): 0.81 (6H, d, J=7Hz), 1.75 (1H, m), 2.44 (2H, d, J=7Hz), 3.78 (2H, s), 7.0-8.0 (9H, m), 10.55 (1H,s); MS: 323 (M+)
Anal. Calc'd. for $C_{20}H_{21}NOS$: C, 74.30; H, 6.50; N, 4.33.
Found: C, 74,68; H, 6.47; N, 4.37.

Example 4. 2-[1-(4-isobutylphenyl)propyl]-5-phenyl-4-hydroxythiazole (Formula I, Z = 2-[1-(4-isobutylphenyl)propyl], R_1= phenyl, M= H).

The title compound was prepared according to the method of Example 1 except that butibufen was used instead of naproxen.

mp 168-169°C; ^{1}H NMR (60 MHz,DMSO-d_6): 0.85 (3H, d, J=7Hz), 0.91 (3H, t, J=7Hz), 1.58 (2H, m), 1.85 (1H, m), 2.45 (2H, d, J=7Hz), 4.02 (1H, t, J=7Hz), 7.0-8.0 (9H, m), 10.55 (1H, s); MS: 351 (M+)
Anal. Calc'd. for $C_{22}H_{25}NOS$: C,75.21; H, 7.12; N, 3.99.
Found: C, 74.98; H, 7.14; N, 4.10.

Example 5. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= phenyl, M= H).

Methyl diethylphosphonoacetate (1.6 g, 7.5 mmol) and NaH (0.19 g, 7.5mmol) in THF (25mL) was added to 2-acetyl-6-methoxynaphthalene (1.5 g, 7.5mmol) in THF (50 mL) at 23° C under nitrogen. After refluxing for 20 hours, the reaction mixture was cooled, saturated NH_4Cl added,and the mixture poured into water. The solution was extracted with ether and the organic extracts were dried ($MgSO_4$) and the solvent evaporated. Chromatography (silica gel, ether/pentane) afforded methyl 3-(6-methoxy-2-naphthyl)-2-butenoate (0.75g). This intermediate (0.51 g, 2 mmol) in methanol (50 mL) was hydrogenated with 20% Pd/C (50 mg) at 3 atm at 23°C until the theoretical amount of hydrogen was taken up. Removal of solvent and catalyst gave the crude ester which was dissolved in isopropanol/water : 2/1 (40 mL). Lithium hydroxide (82 mg, 2 mmol) was added and the reaction mixture stirred at 23°C for 1 hour. Saturated ammonium chloride was added and the mixture extracted with ethyl acetate. Removal of solvent followed by recrystallization from methanol/water gave 3-(6-methoxy-2-naphthyl) butyric acid (0.45g). Bromine (3 mL of a 1M solution in CCl_4, 3 mmol) was added slowly to the acid (0.37 g, 1.5 mmol) and PBr_3 (0.4 g, 1.5 mmol) in CCl_4 (20

mL) at 23°C under nitrogen. The mixture was heated at 80° C for 20 hours. The mixture was then cooled and poured into ice water. Extraction with benzene followed by drying (Na_2SO_4) and evaporation gave a crude residue which was distilled under reduced pressure (0.5 mm) to afford 2-bromo-3-(6-methoxy-2-naphthyl)-butyrylbromide (0.55g). ^1H NMR(60 MHz, DMSO-d6): 1.30 (3H, d J=7 Hz), 3.80 (3H, s), 4.01 (1H, q, J=7Hz), 4.20 (1H, d, J=7Hz), 7.0-8.0 (6H, m); Mass Spectrum: 386(M+)

Anal. Calc'd for $C_{15}H_{14}Br_2O_2$: C,46.63; H, 3.63.
Found: C, 46.87; H, 3.59.

To a solution of 2-bromo-3-(6-methoxy-2-naphthyl) butyrylbromide (386 mg, 1 mmol) in toluene (20 mL) was added thiobenzamide (137 mg, 1 mmol) and pyridine (0.16 mL, 2 mmol) in toluene (60 mL) at 23°C. The reaction mixture was heated at 100°C for 4 hours and then cooled and the solvent removed in vacuo. Recrystallization of the residue from ethanol/ether provided the desired product (128 mg). mp 224-226°C, ^1H NMR (60 MHz, DMSO-d_6): 1.30 (3H, d, J=7 Hz), 3.82 (3H, s), 3.92 (1H, q, J=7 Hz), 7.1-8.0 (11H, m), 10.55 (1H, s); Mass Spectrum: 361 (M+)

Anal. Calc'd for $C_{22}H_{19}NO_2S$: C, 73.12, H, 5.26; N, 3.88.
Found: C, 72.89; H, 5.27; N, 4.01.

Example 6. 2-[1-(6-methoxy-2-naphthyl)ethyl]-5-(4-methoxyphenyl)-4-hydroxythiazole (Formula I, Z= 1-(6-methoxy-2-naphthyl)ethyl, R_1= 4-methoxyphenyl, M= H).

The desired compound is prepared according to the method of Example 1 except using 2-chloro-2-(4'-methoxyphenyl)acetylchloride instead of alpha-chlorophenylacetylchloride.

Example 7. 2-[1-(6-methoxy-2-naphthyl)ethyl]-5-(4-carbomethoxyphenyl)-4-hydroxythiazole (Formula I, Z= 1-(6-methoxy-2-naphthyl)ethyl, R_1= 4-carbomethoxy-phenyl, M= H).

The desired compound is prepared according to the method of Example 1 except using 2-chloro-2-(4'-carbomethoxyphenyl)acetylchloride instead of alpha-chlorophenylacetylchloride.

Example 8. 2-[1-(4-isobutylphenyl)propyl]-5-(4-methoxyphenyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-methoxyphenyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-(4'-methoxyphenyl)acetylchloride instead of alpha-chlorophenylacetylchloride.

Example 9. 2-[1-(4-isobutylphenyl)propyl]-5-(4-methoxycarbonylphenyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-methoxy-carbonylphenyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-(4'-methoxycarbonylphenyl)acetylchloride instead of alpha-chlorophenylacetylchloride.

Example 10. 2-[1-(4-isobutylphenyl)propyl]-5-(4-fluorophenyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-fluorophenyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-(4'-fluorophenyl)acetylchloride instead of alpha-chlorophenylacetylchloride.

Example 11. 2-[1-(4-isobutylphenyl)propyl]-5-(2.4-difluorophenyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 2,4-difluorophenyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-(2,4-difluorophenyl)acetylchloride instead of alpha-chlorophenylacetylchloride.

Example 12. 2-[1-(4-isobutylphenyl)propyl]-5-propyl-4-hydroxythiazole (Formula I, Z = 2-[1-(4-isobutylphenyl)propyl], R_1= propyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloropentanoyl chloride instead of alpha-chlorophenylacetylchloride.

Example 13. 2-[1-(4-isobutylphenyl)propyl]-5-(1-ethylphenyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 1-ethylphenyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-4-phenylbutyrylchloride instead of alpha-chlorophenylacetylchloride.

Example 14. 2-[1-(4-isobutylphenyl)propyl]-5-(1-ethenylphenyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 1-ethenylphenyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-4-phenylbut-3-enoylchloride instead of alpha-chlorophenylacetylchloride.

Example 15. 2-[1-(4-isobutylphenyl)propyl]-5-cyclohexyl-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= cyclohexyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-cyclohexyl-acetylchloride instead of alpha-chlorophenyl-acetylchloride.

Example 16. 2-[1-(4-isobutylphenyl)propyl]-5-cyclopropyl-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= cyclopropyl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-cyclopropyl-acetylchloride instead of alpha-chlorophenyl-acetylchloride.

Example 17. 2-[1-(4-isobutylphenyl)propyl]-5-(thien-2-yl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= thien-2-yl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-2-thienyl-acetylchloride instead of alpha-chlorophenyl-acetylchloride.

Example 18. 2-[1-(4-isobutylphenyl)propyl]-5-(methylthien-2-yl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= methylthien-2-yl, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-3-(thien-2-yl)propionylchloride instead of alpha-chlorophenylacetylchloride.

Example 19. 2-[1-(4-isobutylphenyl)propyl]-5-[3-(ethoxycarbonyl)propyl]-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 3-(ethoxycarbonyl)propyl, or $-(CH_2)_3C(O)OEt$, M= H).

The desired compound is prepared according to the method of Example 4 except using 2-chloro-6-ethoxy-

carbonylhexanoylchloride instead of alpha-chlorophenyl-acetylchloride.

Example 20. 2-[1-(4-isobutylphenyl)propyl]-5-(4-N-methyl-N-hydroxyamidobutyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-N-methyl-N-hydroxyamidobutyl, M= H).

The desired compound is prepared by treatment of the product of Example 19 with N-methylhydroxylamine hydrochloride.

Example 21. 2-[1-(4-isobutylphenyl)propyl]-5-(4-hydroxybutyl)-4-hydroxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-hydroxybutyl, M= H).

The desired compound is prepared from the product of Example 19 by reduction with $LiBH_4$.

Example 22. 2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-acetylthiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-phenyl, M= $COCH_3$).

The desired compound is prepared by treatment of the product of Example 4 with acetic annydride and pyridine.

Example 23. 2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-hydroxythiazole potassium salt (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-phenyl, M= K).

The desired compound is prepared by treatment of the product of Example 4 with potassium hydroxide.

Example 24. 2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-trimethylsilyloxythiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-phenyl, M= $Si(CH_3)_3$).

The desired compound is prepared by treatment of the product of Example 4 with trimethylsilylimidazole.

Example 25. 2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-glycinylthiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-phenyl, M= $COCH_2NH_2$).

The desired compound is prepared by treatment of the product of Example 4 with N-BOC glycine and DCC followed by cleavage of the BOC group by standard methods.

Example 26. 2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-succinylthiazole (Formula I, Z= 2-[1-(4-isobutylphenyl)propyl], R_1= 4-phenyl, M= $COCH_2CH_2COOH$).

The desired compound is prepared by treatment of the product of Example 4 with succinyl anhydride.

Example 27. 2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-succinyl-N-methyl-N-hydroxyamidothiazole (Formula I, Z = 2-[1-(4-isobutylphenyl)propyl], R_1= 4-phenyl, M= $COCH_2CH_2CON(CH_3)OH$).

The desired compound is prepared by treatment of the product of Example 22 with oxalyl choride followed by N-methylhydroxylamine.

Example 28. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-fluorophenyl-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 4-fluoro-phenyl, M= H).

The desired compound is prepared according to the method of Example 5 using 4-fluorothiobenzamide instead of thiobenzamide.

Example 29. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2,4-difluorophenyl-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 2,4-difluorophenyl, M= H).

The desired compound is prepared according to the method of Example 5 using 2,4-difluorothiobenzamide instead of thiobenzamide.

Example 30. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-methoxyphenyl-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 4-methoxyphenyl, M= H).

The desired compound is prepared according to the method of Example 5 using 4-methoxythiobenzamide instead of thiobenzamide.

Example 31. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(thien-3-yl)-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= thien-3-yl, M= H).

The desired compound is prepared according to the method of Example 5 using 3-thioamidothiophene instead of thiobenzamide.

Example 32. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-pyridyl)-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 4-pyridyl, M= H).

The desired compound is prepared according to the method of Example 5 using 4-thioamidopyridine instead of thiobenzamide.

Example 33. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-pyridyl)-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 2-pyridyl, M= H).

The desired compound is prepared according to the

method of Example 5 using 2-thioamidopyridine instead of thiobenzamide.

Example 34. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-benzothienyl)-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 2-benzothienyl, M= H).

The desired compound is prepared according to the method of Example 5 using 2-thioamidobenzothiophene instead of thiobenzamide.

Example 35. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-benzothiazoyl)-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 2-benzothiazole, M= H).

The desired compound is prepared according to the method of Example 5 using 2-thioamidobenzothiazole instead of thiobenzamide.

Example 36. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-thiazoyl)-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= 2-thiazole, M= H).

The desired compound is prepared according to the method of Example 5 using 2-thioamidothiazole instead of thiobenzamide.

Example 37. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-acetoxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= phenyl, M= $COCH_3$).

The desired compound is prepared by treatment of the product of Example 5 with acetic anhydride and pyridine.

Example 38. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole potassium salt (Formula II, Z=

5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= phenyl, M= $COCH_3$).

The desired compound is prepared by treatment of the product of Example 5 with potassium hydroxide.

Example 39. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-methoxycarbonyloxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= phenyl, M= $COOCH_3$).

The desired compound is prepared by treatment of the product of Example 5 with chloromethylformate and pyridine.

Example 40. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-N-methyl-N-hydroxycarbonyl-oxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= phenyl, M= $CON(CH_3)OH$.

The desired compound is prepared by treatment of the product of Example 5 with phosgene and N-methylhydroxylamine.

Example 41. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-succinylthiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= phenyl, M= $COCH_2CH_2COOH$).

The desired compound is prepared by treatment of the product of Example 5 with succinic anhydride.

Example 42. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-[1-(4-isobutylphenyl)ethyl]-4-acetoxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= [1-(4-isobutylphenyl)ethyl], M= $COCH_3$).

The desired compound is prepared according to the method of Example 5 using thioamidoibuprofen instead of thiobenzamide.

Example 43. 5-[1-(6-methoxy-2-naphthyl)ethyl]-2-[1-(4-isobutylphenyl)propyl]-4-hydroxythiazole (Formula II, Z= 5-[1-(6-methoxy-2-naphthyl)ethyl], R_1= [1-(4-isobutylphenyl)propyl], M= H).

The desired compound is prepared according to the method of Example 5 using thioamidobutibufen instead of thiobenzamide.

Example 44. 2-[1-(4-isobutylphenyl)ethyl]-5-[1-(4-isobutylphenyl)ethyl]-4-hydroxythiazole (Formula II, Z= 5-[1-(4-isobutylphenyl)ethyl], R_1= [1-(4-isobutylphenyl)ethyl], M= H).

The desired compound is prepared according to the method of Scheme II using ibuprofen and thioamidoibuprofen.

Example 45. 2-[1-(6-methoxy-2-naphthyl)ethyl]-5-[1-(4-isobutylphenyl)ethyl]-4-hydroxythiazole (Formula I, Z= 2-[1-(6-methoxy-2-naphthyl)ethyl], R_1= [1-(4-isobutylphenyl)ethyl], M= H).

The desired compound is prepared according to the method of Scheme II using naproxen and thioamidoibuprofen .

Example 46. 2-[1-(6-methoxy-2-naphthyl)ethyl]-5-[1-(4-isobutylphenyl)ethyl]-4-benzoylthiazole (Formula I, Z= 2-[1-(6-methoxy-2-naphthyl)ethyl], R_1= [1-(4-isobutylphenyl)ethyl], M= COC_6H_5)

The desired compound is prepared by treatment of the product of example 45 with benzoyl chloride and pyridine.

Example 47. 2-[1-(4-phenoxyphenyl)ethyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 2-[1-(4-phenoxyphenyl)ethyl], R_1= phenyl, M= H.)

The desired compound is prepared according to the

method of Example 1 using fenoprofen instead of naproxen.

Example 48. 2-[1-(2-(4-chlorophenyl)benzoxaz-5-yl) ethyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 2-[1-(2-(4-chlorophenyl)benzoxaz-5-yl)ethyl], R_1= phenyl, M= H).

The desired compound is prepared according to the method of Example 1 using benoxaprofen instead of naproxen.

Example 49. 2-[2-(4,5-diphenyloxaz-2-yl)ethyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 2-[2-(4,5-diphenyloxaz-2-yl)ethyl], R_1= phenyl, M= H).

The desired compound is prepared according to the method of Example 1 using oxaprozin instead of naproxen.

Example 50. 2-[2-(N-methyl-9-methoxyphenothiazin-4-yl) ethyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 2-[2-(N-methyl-9-methoxyphenothiazin-4-yl)ethyl], R_1= phenyl, M= H).

The desired compound is prepared according to the method of Example 1 using protizinic acid instead of naproxen.

Example 51. 2-[5-fluoro-2-methyl-(4-methylsulfinyl-benzylidene)-inden-3-ylmethyl]-5-phenyl-4-hydroxythiazole (Formula I, Z= 2-[5-fluoro-2-methyl-(4-methylsulfinyl benzylidene)-inden-3-ylmethyl], R_1= phenyl, M= H).

The desired compound is prepared according to the method of Example 1 using sulindac instead of naproxen.

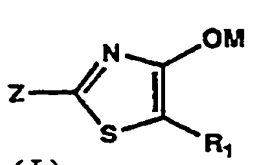
Inhibition of 5-Lipoxygenase

Inhibition of 5-lipoxygenase activity was determined using the 20,000x g supernatant from homogenized RBL-1 cells in a similar manner as that described by Dyer and coworkers (Dyer, R.D.; Haviv, F.; Hanel, A.M.; Bornemier, D.A.; Carter, G.W. Fed. Proc., Fed. Am. Soc. Exp. Biol., 43:1462A, (1984).) IC_{50} values (concentration of compound producing 50% enzyme inhibition) were calculated by linear regression analysis of percentage inhibition versus log inhibitor concentration plots.

EXAMPLE	IC_{50} (10^{-6}M)	95% Confidence Limits (10^{-6}M)
1	0.42	0.36 - 0.47
2	0.71	0.68 - 0.74
3	1.1	1.0 - 1.2
4	0.06	0.05 - 0.07
5	0.9	0.6 - 1.2

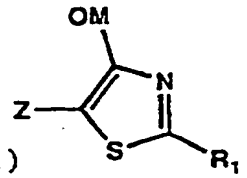
WHAT IS CLAIMED IS:

1. A compound of the formula



(I)

or



(II)

wherein R_1 is selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, reduced heteroaryl and reduced heteroarylalkyl, and substituted derivatives thereof wherein the substituents are independently chosen from the group consisting of halogen, alkyl, halosubstituted alkyl, aryl, arylalkyl, reduced heteroaryl, arylalkoxy, cyano, nitro, $-C(O)R_4$, $-SO_2R_4$, $-NR_5R_6$, $-OR_6$, $-C(O)CX_1X_2NR_6R_7$, $-C(O)N(OH)R_6$, $-NR_6C(O)R_4$, $-CR_5(NH_2)CO_2R_5$, $-NHCX_1X_2CO_2R_5$, $-N(OH)C(O)NR_5R_6$, $-N(OH)C(O)R_4$, $-NHC(O)NR_5R_6$, $-C(NOH)NHOH$ and $-C(O)NHNR_5R_6$;

R_4 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, reduced heteroaryl, reduced heteroarylalkyl, $-OR_5$, $-NHCX_1X_2CO_2R_5$ and $-NR_6R_7$;

R_5 is selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, reduced heteroaryl and reduced heteroarylalkyl;

R_6 and R_7 is independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl, arylalkyl, reduced heteroaryl, reduced heteroarylalkyl and $-(CH_2)_nOR_5$ wherein n is 2 to 4;

X_1 and X_2 are independently selected from hydrogen, alkyl, alkenyl, cycloalkyl, aryl and arylalkyl;

M is selected from hydrogen, a pharmaceutically acceptable cation, $-COR_4$, $-C(O)CX_1X_2NR_6R_7$, $-CR_8R_9OR_{10}$, $-CH_2CR_8(OR_{10})CH_2OR_{11}$, and $-SiR_{12}R_{13}R_{14}$;

R_8, R_9, R_{10} and R_{11} are independently selected from hydrogen, alkyl, aryl, arylalkyl, $-(CH_2)_nOR_5$ wherein n is 2 to 4, or at least two of R_8, R_9, R_{10} and R_{11} together form a carbocyclic or heterocyclic or reduced heterocyclic ring system containing 5 to 10 atoms;

R_{12}, R_{13} and R_{14} are independently selected from alkyl and aryl; and

Z is a residue of a non-steroidal antiinflammatory drug;

or a pharmaceutically acceptable salt, ester or prodrug thereof.

2. The compound according to Claim 1 wherein R_1 is selected from propyl, cyclopropyl, cyclohexyl, phenyl, 4-phenyl, 4-fluorophenyl, 2,4-difluorophenyl, 1-ethylphenyl, 4-methoxyphenyl, 4-carbomethoxyphenyl, 4-methoxycarbonylphenyl, thien-2-yl, thien-3-yl, methylthien-2-yl, 2-benzothienyl, 2-thiazole, 2-benzothiazole, 2-pyridyl, 4-pyridyl, 4-hydroxybutyl, 4-N-methyl-N-hydroxyamidobutyl, 3-(ethoxycarbonyl)propyl, 1-(4-isobutylphenyl)ethyl and 1-(4-phenoxyphenyl)ethyl.

3. The compound according to Claim 1 wherein Z is selected from benoxaprofen, benzofenac, bucloxic acid, butibufen, carprofen, cicloprofen, cinmetacin, clidanac, clopirac, diclofenac, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flunoxaprofen, furaprofen, furobufen, furofenac, ibuprofen, ibufenac, indomethacin, indoprofen, isoxepac, ketoprofen, lonazolac, metiazinic, miroprofen, naproxen, oxaprozin, oxepinac,

pirprofen, pirazolac, protizinic acid, sulindac, suprofen, tiaprofenic acid, tolmetin, and zomepirac.

4. The compound according to Claim 1 wherein R_1 is phenyl and M is hydrogen.

5. A compound selected from the following:

2-[1-(6-methoxy-2-naphthyl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[(4-isobutylphenyl)methyl]-5-phenyl-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-phenyl-4-hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole;
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-(4-methoxyphenyl)-4-hydroxythiazole;
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-(4-carbomethoxy-phenyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-methoxyphenyl)--4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-methoxycarbonyl-phenyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-fluorophenyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(2,4-difluorophenyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(propyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(1-ethylphenyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(1-ethenylphenyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-cyclohexyl-4-hydroxythiazole;

2-[1-(4-isobutylphenyl)propyl]-5-cyclopropyl-
4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(thien-2-yl)-
4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(methylthien-2-yl)-4-
hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-[3-(ethoxycarbonyl)propyl]-
4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-N-methyl-N-
hydroxyamidobutyl)-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-hydroxybutyl)-
4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-
4-acetylthiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-
4-hydroxythiazole potassium salt;
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-
trimethylsilyloxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-
glycinylthiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-
succinylthiazole;
2-[1-(4-isobutylphenyl)propyl]-5-(4-phenyl)-4-succinyl-
N-methyl-N-hydroxyamidothiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-fluorophenyl-4-
hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2,4-difluorophenyl-
4-hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-methoxyphenyl-4-
hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(thien-3-yl)-4-
hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(4-pyridyl)-4-
hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-pyridyl)-4-
hydroxythiazole;

5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-benzothienyl)-4-hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-benzothiazoyl)-4-hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-(2-thiazoyl)-4-hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-acetoxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole potassium salt;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-methoxycarbonyloxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-N-methyl-N-hydroxycarbonyl-oxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-succinylthiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-[1-(4-isobutyl-phenyl)ethyl]-4-acetoxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-[1-(4-isobutyl-phenyl)propyl]-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)ethyl]-5-[1-(4-isobutylphenyl)-ethyl]-4-hydroxythiazole;
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-[1-(4-isobutyl-phenyl)ethyl]-4-hydroxythiazole;
2-[1-(6-methoxy-2-naphthyl)ethyl]-5-[1-(4-isobutyl-phenyl)ethyl]-4-benzoylthiazole;
2-[1-(4-phenoxyphenyl)ethyl]-5-phenyl-4-hydroxythiazole];
2-[1-(2-(4-chlorophenyl)benzoxaz-5-yl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[2-(4,5 diphenyloxaz-2-yl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[2-(N-methyl-9-methoxyphenothiazin-4-yl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[5-fluoro-2-methyl-(4-methylsulfinylbenzylidene)-inden-3-ylmethyl]-5-phenyl-4-hydroxythiazole; and pharmaceutically acceptable salts, esters and prodrugs thereof.

6. A compound selected from the following:

2-[1-(6-methoxy-2-naphthyl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)ethyl]-5-phenyl-4-hydroxythiazole;
2-[(4-isobutylphenyl)methyl]-5-phenyl-4-hydroxythiazole;
2-[1-(4-isobutylphenyl)propyl]-5-phenyl-4-hydroxythiazole;
5-[1-(6-methoxy-2-naphthyl)ethyl]-2-phenyl-4-hydroxythiazole; and
pharmaceutically acceptable salts, esters and prodrugs thereof.

7. A composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound according to Claim 1.

8. A method of inhibiting lipoxygenase enzymes in a mammal in need of such treatment comprising administering to such mammal a therapeutically effective amount of a compound according to Claim 1.

9. A method of treating asthma, allergic rhinitis, rheumatoid arthritis, gout, psoriasis, acne, atherosclerosis, adult respiratory distress syndrome, inflammatory bowel disease, endotoxin shock, ischemia-induced myocardial injury, or central nervous pathophysiology in a mammal in need of such treatment comprising administering to such mammal a therapeutically effective amount of a compound of Claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/06800

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 31/54, 31/44, 31/425, 31/41 US CL.: 544/38; 546/280; 548/152, 182,186,187,189; 514/225.2,342,367,369,824,825,826,859,863

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	544/38; 546/280; 548/152,182,186,187,189; 514/225.2,342,367, 369,824,825,826,859,863

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with Indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	American Chemical Society Journal, Vol. 106, 1984, by E.J. Corney et al. "Rationally Designed, Patent Competitive Intribitors of Leukotriene Biosynthesis" pp. 1503-1504.	1-9
A	Chemical Abstract, Vol. 101, no. 15, 1984, Nelson, Peter Harold (Syntex (U.S.A.), Inc.), "Arachidonic acid analogs as antiinflammatory and antiallergic agents", abstract no. 101: 130499j.	
A	Chemical Abstract, Vol. 106, no. 3, 1987, Summers, James B., Jr. (Abbott Laboratories), "Lipoxygenase-inhibiting napathylalkenohydrox-amates", abstract no. 106: 18160u.	1-9

* Special categories of cited documents: [13]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
12 FEBRUARY 1991	15 MAR 1991
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	CECILIA SHEN

Form PCT/ISA/210 (second sheet) (May 1986)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ..... because they relate to subject matter [1] not required to be searched by this Authority, namely:

2. [X] Claim numbers 1, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [1], specifically:

"reduced heteroaryl", "reduced heteroarylalkyl" "Heterocyclic", "reduced heterocyclic" or "residue of a non-steroidal antiinflammatory drug" is indefinite and unclear.

3. [ ] Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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